UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
STANISLAUS LAURENS JOHAN WOUTERS,
HEINZ HELMUT RENGGLI, and
DANIELLE ANGELIQUE HORBACH

Appeal No. 2006-3336
Application No. 09/780,205
Technology Center 1600

HEARD: December 13, 2006

Before SCHEINER, ADAMS, and LEBOVITZ, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a monoclonal antibody or a fragment thereof that binds and elutes from its epitope under specifically chosen conditions. The Examiner has rejected the claims as obvious over the prior art, and as lacking enablement for the full scope of the claims. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

The specification describes "antibodies or fragments thereof which bind to an epitope under specifically chosen conditions, and which elute from that epitope under specifically chosen different conditions" (Specification 2: 21-24), such that "the antibodies can be removed at any desired moment" (*id.* at 2: 26-27). "These specifically chosen conditions can for instance be formed by the pH or the ion strength" and "preferably lie within physiologically acceptable limits" (*id.* at 3: 20-24).

"An example of an application of antibodies according to the invention is bringing antimicrobial compounds into contact with species of [ ] oral microflora" (*id.* at 4: 21-24) that "make[ ] a significant contribution toward the forming of plaque" (*id.* at 4: 30-31). "For use in the oral cavity the [specifically chosen] pH can for instance be varied between 4 and 8.5 and the ion strength between 0 and 13 M" (*id.* at 3: 24-26).

DISCUSSION

Claims 2, 9, 10, 13-22, 24, 27-31, 35, 40, and 42-49 are the subject of appeal. Claims 23, 25, and 26 are also pending, but have been withdrawn from consideration. Claims 40 and 42 are representative and read as follows:

40. A selected monoclonal antibody, or fragment thereof, wherein:
the selected monoclonal antibody, or fragment thereof, has been selected for its ability to bind to an epitope at a first pH of 8.5; and
the selected monoclonal antibody, or fragment thereof, has also been selected such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 7.

42. A selected monoclonal antibody, or fragment thereof, wherein:
the selected monoclonal antibody, or fragment thereof, has been selected for its ability to bind an epitope at a first pH of 8.5; and

the selected monoclonal antibody, or fragment thereof, has also been selected such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 4.5 and an ion strength of 1M NaCl.

The Examiner relies on the following prior art:

Simonson	4,138,476	Feb. 6, 1979
Beggs	5,490,988	Feb. 13, 1996
Fischer	5,571,511	Nov. 5, 1996
Cummins	EP 0736544	Oct. 9, 1996

Cole et al., "Humoral Immunity to Commensal Oral Bacteria: Avidity of Serum IgG and IgM Antibodies Reactive with *Porphyromonas (Bacteroides) gingivalis* in Children," *Immunology and Infectious Diseases* 3: 33-35 (1993).

JAMES W. GODING, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE 44-45, 231, (2d ed. 1986).

The claims stand rejected as follows:

I. Claims 2, 9, 10, 13-22, 28, 30, 31, 35, 40, and 42-49 under 35 U.S.C. § 103(a) as unpatentable over Beggs and Goding.

II. Claim 29 under 35 U.S.C. § 103(a) as unpatentable over Beggs, Goding, and Cole.

III. Claims 43 under 35 U.S.C. § 103(a) as unpatentable over Beggs, Goding, and Fischer.

IV. Claims 2, 9, 10, 13-21, 24, 27, 28, 30, 31, 35, 40, and 42-49 under 35 U.S.C. § 103(a) as unpatentable over Cummins and Goding.

V. Claims 2, 9, 10, 13-22, 24, 27-31, 35, 40, and 42-49 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims.

Obviousness

Rejections I, II, and III are all based, at least in part, on the combined teachings of Beggs and Goding, so we will discuss the three rejections together. Claims 40 and 42, which represent the invention in its broadest aspect, require a monoclonal antibody or fragment thereof that binds an unspecified epitope at pH 8.5, and elutes at pH 7 (claim 40), or at pH 4.5 and 1M NaCl (claim 42). Claim 29 specifies that the monoclonal antibody or fragment thereof is specific for an epitope on one of several pathogenic microorganisms, while claim 43 specifies it is specific for an epitope of *Staphylococcus epidermidis*.

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

> A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all facts must be considered. The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis. To the extent the Patent Office rulings *are* so supported, there is no basis for resolving doubts against their correctness. Likewise, we may not resolve doubts in favor of the Patent Office determination when there are deficiencies in the record as to the necessary factual bases supporting its legal conclusion of obviousness."

In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967) (emphasis in original).

Beggs describes "an antibody fragment for binding to a target site, and provides for a therapeutic agent to be connected onto the antibody fragment

. . . thereby to attach the agent to the target site." Beggs, col. 1: 59-63. The antibody fragments can be used "for delivery [of therapeutic agents] to target sites which are accessible by topical application" (*id.* at col. 3: 45-46), for example, "target sites in the mouth" (*id.* at col. 3: 50-51), particularly "supragingival oral microflora" (*id.* at col. 3: 54-55). Finally, Beggs teaches "[f]or [ ] oral applications (dental care) it would be appropriate for the vehicle(s) in the product to be suitable for topical application in the mouth" (*id.* at col. 4: 31-33).

Goding teaches that "monoclonal antibod[y] [binding] may be very susceptible to minor changes" in pH and salt concentration (Goding at 44-45), and describes one particular monoclonal antibody that "bound its antigen at pH 7.0 and at salt concentrations of less than 100 mM, but at pH 8.0 and 200 mM NaCl, binding was virtually abolished" (*id.* at 45). On the other hand, Goding teaches that "[o]ther monoclonal antibodies . . . may require very harsh conditions (e.g. pH 2.0, 3.5 M KSCN or 7 M guanidine-HCl) before the antigen-antibody bond is disrupted" (*id.*). Under the heading "Elution of Antigen from Immunoadsorbents" (*id.* at 231), Goding teaches that "[t]he most popular method of elution of antibodies or antigens from immune complexes involves the use of glycine-HCl buffers at pH 2.2-2.8" and "[m]ost antibodies will release their antigen under these conditions" (*id.*). If not, "a trial of elution at pH 11.5 [ ] may be rewarding" (*id.*).

The Examiner finds that Beggs describes "antibod[ies] [and] . . . fragments that are able to bind to a target site through antibody-antigen binding at conditions [that] lie within physiologically acceptable limits." Answer 6. According to the Examiner, a "pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits" (*id.*). The Examiner further finds that Goding teaches that "it is an inherent propert[y] of all antibod[ies] and fragment[s] to bind to an epitope under one set of specifically chosen conditions and be eluted

from an epitope . . . under specifically chosen different conditions" (*id.* at 6-7). Therefore, "[i]t would have been obvious to one of ordinary skill in the art . . . to determine all operable and optimal range[s] of pH and ion strength at which antibody or fragment thereof binds to and elute[s] from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by Beggs" (*id.* at 7), where "some advantage or expected beneficial result would have been produced" (*id.*).

If we understand the Examiner's rationale, it is that Beggs describes monoclonal antibodies or fragments that inherently have the properties required by the claims. One problem with the Examiner's rationale is that Beggs' description of suitable antibodies and fragments is purely hypothetical, and even then, is couched only in terms of specificity for a given target. Beggs says nothing at all about antibodies that bind at a particular pH, much less antibodies that elute at a particular pH. Even if we were to accept that one skilled in the art would have understood Beggs to require antibodies that bind within physiological limits (which the Examiner asserts is a pH between 6 and 8), the Examiner does not explain how that supports an assertion that Beggs' antibodies inherently bind at pH 8.5 and elute at pH 7.

To establish that a reference inherently discloses a specific limitation, the Examiner may refer to extrinsic evidence demonstrating that the descriptive matter missing from the reference is necessarily present in the reference's disclosure. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). ("[W]hen the reference is silent about the asserted inherent characteristic, [a] gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so

recognized by persons of ordinary skill."). Presumably, this was the Examiner's purpose in citing Goding.

However, the Examiner cannot establish inherency merely by demonstrating that the asserted limitation is probable or possible. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient") (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939) (emphasis in original). Again, Beggs' antibodies are purely hypothetical.

Nor has the Examiner identified anything in Beggs or Goding that would have led one skilled in the art to select antibodies or fragments with the particular properties recited in the claims. Beggs says nothing at all about eluting antibody from the target, and the only pHs Goding mentions with respect to elution are pH 8, pH 2, pH 2.2-2.8, and pH 11.5.

The Examiner has not established an adequate factual basis for rejecting claims 40 and 42, the broadest claims on appeal. We cannot emphasize enough that the Examiner may not "resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in [the] factual basis" of the rejection (*Warner*, 379 F.2d at 1017, 154 USPQ at 178). On this record, we are constrained to reverse the rejection of claims 2, 9, 10, 13-22, 28, 30, 31, 35, 40, and 42-49 under 35 U.S.C. § 103(a) as unpatentable over Beggs and Goding (Rejection I).

Cole and Fischer, the additional references relied on by the Examiner in rejecting claims 29 and 43, respectively, do not cure the underlying deficiencies of the proposed combination of Beggs and Goding. Accordingly, we reverse the rejections of claims 29 and 43 under 35 U.S.C. § 103(a) (Rejections II and III) as well.

Rejection IV is based on the combined teachings of Cummins and Goding. Goding is discussed above. Cummins describes several monoclonal antibodies specific for cryptotopes on salivary pellicle. Cummins 6-10. The antibodies are useful in "delivery of oral care active agents" (*id.* 3: 16). They "are substantive (i.e. withstand the flow of saliva), are not inhibited by soluble salivary components and remain reactive . . . in the presence of a developing biofilm" (*id.* at 3: 30-31).

The Examiner finds that Cummins "teach[es] various binding conditions that lie within physiologically acceptable limits, including pH and ion strength" (Answer 8), based on Cummins' teaching that "[b]uffers and salts to buffer the pH and ionic strength of the [antibody] compositions may also be included" (Cummins 4: 39). The Examiner finds that a "pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits" (Answer 8). Therefore, "[i]t would have been obvious to one of ordinary skill in the art . . . to determine all operable and optimal range[s] of pH and ion strength at which antibody or fragment thereof binds to and elute[s] from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by[ ] Cummins" (*id.* at 9), where "some advantage or expected beneficial result would have been produced" (*id.*).

Again, if we understand the Examiner's rationale, it is that Cummins describes antibodies that inherently have the properties required by the claims. Nevertheless, the Examiner has not identified anything in the reference that would indicate that Cummins' antibodies bind at pH 8.5 and elute at the required pHs. Again, inherency cannot be established merely by asserting that the required properties are possible. Nor has the Examiner identified anything in Cummins or Goding that would have led one skilled in the art to select antibodies or fragments with the particular properties recited in the claims. Cummins says nothing at all

about eluting antibody from the target, and the only pHs Goding mentions with respect to elution are pH 8, pH 2, pH 2.2-2.8, and pH 11.5.

The Examiner has not established an adequate factual basis for rejecting claims 40 and 42, the broadest claims on appeal, on the basis of Cummins and Goding. Accordingly, the rejection of claims 2, 9, 10, 13-21, 24, 27, 28, 30, 31, 35, 40, and 42-49 under 35 U.S.C. § 103(a) as unpatentable over Cummins and Goding (Rejection IV) is reversed.

Scope of Enablement

Essentially, the Examiner's position is that the specification does not enable one of skill in the art to isolate antibodies by any means "other than [the] specifically chosen conditions recited in Table 1" (Answer 4), or to use such antibodies for anything other than "detection of dental plaque or other oral pathogens" (*id.*, page 5). According to the Examiner, "the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue" (*id.*).

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Whether the amount of experimentation required is undue is determined by reference to the well-known *Wands* factors. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The fact that a considerable amount of experimentation may be required to practice the invention does not preclude enablement, if it is merely routine, or if the specification provides a reasonable amount of guidance as to its direction. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir.

1996), citing *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). Moreover, "[A]ppellants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976).

The only explanation offered by the Examiner in support of his assertion that it would have required undue experimentation to obtain antibodies (other than those described in the specification) capable of binding an epitope at pH 8.5 and eluting at pH 7 (or at pH 4.5 and 1 M NaCl) is that "only *16 specific clones* out of [an] entire phage display library, which includes *at the very least, millions of candidate* monoclonal antibodies, [ ] possess the required specific characteristics" (Answer 4, emphasis in original).

Nevertheless, the specification teaches that "[a]n antibody according to the invention is selected using the [ ] known 'phage-display' technique" (*id.* at 2: 34-36), and that "[t]here are large [ ] phage libraries (or banks) of . . . fragments [ ] with different antibody specificities" (*id.* at 3: 11-13). "Such phage libraries are used in the present invention to select [ ] antibody fragments . . . [that] bind to a determined epitope under specifically chosen conditions and that . . . [elute under] specifically chosen different conditions" (*id.* at 3: 11-19).

Given the guidance and direction set forth in the specification, the Examiner has not explained why isolating additional antibodies with the properties required by the claims would require anything more than routine, iterative experimentation, using existing phage libraries or banks of fragments, etc.

Finally, the Examiner acknowledges that the claimed antibodies are enabled "for removing the dye . . . used for the detection of dental plaque or other oral pathogens" (Answer 5, emphasis omitted), but argues that the specification "does

not adequately teach . . . other benefits of the antibody[ies] or fragments" (*id.*). Nevertheless, we know of no requirement that the specification enable more than one use of a claimed product. In any case, the specification indicates that the antibodies can be used "in the targeted and temporary diagnostic, therapeutic and cosmetic treatment of externally accessible parts of the human and animal body" (Specification 1).

On the facts of this case, we find that the Examiner has not adequately explained why practicing the full scope of the claims would have required undue experimentation. The rejection of claims 2, 9, 10, 13-22, 24, 27-31, 35, 40, and 42-49 for lack of enablement is reversed.

OTHER ISSUES

Claim 40 merely requires a monoclonal antibody, *any* monoclonal antibody that binds its epitope at pH 8.5, and elutes from the epitope at pH 7. Most of the remaining claims are not much narrower. It appears that the Examiner, in focusing on the intended methods of use described in the specification, may not have appreciated the true breadth of the claims, and the search of the prior art may have been unduly restrictive.

Finally, we note that claims 44-47 do not further limit the claims from which they depend.

SUMMARY

The rejections of the claims under 35 U.S.C. §§ 103(a) and 112, first paragraph, are reversed.

REVERSED

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